REMARKS/ARGUMENTS

By this Amendment, claims 3-4 are amended, and claims 5-7 are added. Claims 1-7 are pending.

Citations to the Specification are directed to U.S. Patent Application No. 2005/0222208 (Parthasaradhi et al.). Support for new claims 5-7 can be found throughout the Specification as filed, and specifically: support for new claims 5-7 can be found in ¶[0011] to ¶[0014]. No new matter has been added by this amendment.

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Rejection under 35 USC 112 first paragraph

Claims 1-4 stand rejected under 35 U.S.C. 112, first paragraph, allegedly because the specification, while being enabling for using solvents of methanol/ethanol:$CHCl_3$ in 1.2-1 v/v, does not reasonably provide enablement for the claimed scope of unlimited combination of alcohol selected from the group consisting of methanol, ethanol, isopropyl alcohol, tert-butyl alcohol and n-butyl alcohol and the chlorinated solvent selected from the group consisting of chloroform, methylene dichloride, carbontetrachloride and ethylene dichloride with any and all ratio. The Examiner alleges that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to operate the invention commensurate in scope with these claims. This rejection is respectfully traversed.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. United States v. Telectronics, Inc., 857 F.2d 778, 785 (Fed. Cir. 1988). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 USC 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. In re Marzocchi, 439 F.2d 220, 224 (CCPA 1971).

However, here, the claims are enabled because there is not any reason to doubt the

objective truth of the statements contained in the Specification for enabling support. The Specification discloses the manner and process for making and using the claimed invention, including working examples which show the efficacy of the claimed invention.

The Examiner cites the O'Hara reference as allegedly optimization of solvent evaporation is an unpredictable parameter in experimentation of spray drying process in production. However, the Specification discloses a method wherein donepezil hydrochloride is dissolved in the mixture of methanol and chloroform and the solution is subjected to vacuum drying to give amorphous donepezil hydrochloride (see Example 1, ¶[0011]), and further discloses subjecting the solution to spray drying instead of vacuum drying using nitrogen gas to give amorphous donepezil hydrochloride (see Example 2, ¶[0012]). The Specification further discloses crystalline donepezil hydrochloride dissolved in a mixture of ethanol and chloroform and this solution is subjected to vacuum drying to give amorphous donepezil hydrochloride (see Example 3, ¶[0013]) and further discloses subjecting the solution to spray drying instead of vacuum drying using nitrogen gas to give amorphous donepezil hydrochloride (see Example 4, ¶[0014]).

Thus, given the teachings of the Specification, the quantity of experimentation required is not excessive in view of the subject matter of the claims. The Specification sets forth several methods for producing amorphous donepezil hydrochloride. Working Examples are provided, including working examples of spray drying, as well as detailed information as to the methods. This information can be used by one of ordinary skill in the art to determine appropriate solution conditions to practice the claimed process, without undue experimentation.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 USC 102(e)

Claims 1 and 4 stand rejected under 35 USC 102(e) over Vidyadhar et al. (U.S. Patent No. 6,649,765). This rejection is respectfully traversed.

The Examiner sets forth that Applicants argued that the prior art does not anticipate because it does not inherently contain applicants' "mixture". The Examiner sets forth that this is erroneous with respect to claims 1 or 4 because no limitation was found in the claims. The Examiner sets forth that Applicants provided no evidence that the residue $MeCl_2$ in MeOH formed in situ in the prior art has any difference between a mixture of adding the two solvent.

The Examiner sets forth that the CRC handbook and '842 references provided factual verification that indeed the inherent nature was found.

In Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) (MPEP 2131), the CAFC set forth that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference". In the instant case, not every element of the claims is present in the Vidyadhar patent.

The claims are directed to a process for preparation of amorphous donepezil hydrochloride, which comprises dissolving donepezil hydrochloride in a mixture of an alcohol and a chlorinated solvent; and removing the solvents from the solution; wherein the alcohol is selected from the group consisting of methanol, ethanol, isopropyl alcohol, tert-butyl alcohol and n-butyl alcohol and the chlorinated solvent is selected from the group consisting of chloroform, methylene dichloride, carbontetrachloride and ethylene dichloride.

In contrast, the '765 Vidyadhar patent discloses preparing donepezil free base in methylene chloride, then removing the methylene chloride (see Example 2). In an additional step, the donepezil free base is dissolved in methanol, followed by addition of hydrochloric acid. So, there is not a disclosure in the '765 Vidyadhar patent of a process wherein donepezil hydrochloride dissolved in a mixture of an alcohol and a chlorinated solvent.

The Examiner argues that no limitation was found in the claims for a "mixture". However, claim 1 recites that the process "comprises dissolving donepezil hydrochloride in a mixture of an alcohol and a chlorinated solvent". This limitation is clearly not disclosed in the Vidyadhar patent, which instead discloses donepezil free base dissolved in methylene chloride, then removing the methylene chloride. There is an additional step wherein methanol is added, but there is never a mixture.

The Examiner asserts that no evidence that the residue MeCl2 in MeOH formed in situ in the prior art has any difference between a mixture of adding the two solvents has been provided and alleges that the CRC handbook and '842 references provided factual verification that indeed the inherent nature was found.

However, the disclosure of the '842 patent does not disclose that the product of the '765 patent is amorphous, and the CRC reference simply defines the term "amorphous". However, if

the Examiner is arguing that the Vidyadhar patent inherently discloses that the residue MeCl2 in MeOH formed in situ disclosed by Vidyadhar is the same as a mixture comprising the two solvents, then the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' "In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). Here, the Examiner has not met that burden by arguing that Applicant needs to show a difference. "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

If the Examiner is aware of, or alleges to have some knowledge that the residue MeCl2 in MeOH formed in situ allegedly disclosed by Vidyadhar are the same as a mixture comprising the two solvents then the Examiner should provide such knowledge It would not be appropriate for the Examiner to take official notice of facts without citing a prior art reference where the facts asserted to be well known are not capable of instant and unquestionable demonstration as being well-known. For example, assertions of technical facts in the areas of esoteric technology or specific knowledge of the prior art must always be supported by citation to some reference work recognized as standard in the pertinent art. In re Ahlert, 424 F.2d at 1091, 165 USPQ at 420-21. If applicant adequately traverses the examiner's assertion of official notice, the examiner must provide documentary evidence in the next Office action if the rejection is to be maintained. See 37 CFR 1.104(c)(2). See also Zurko, 258 F.3d at 1386, 59 USPQ2d at 1697 ("[T]he Board [or examiner] must point to some concrete evidence in the record in support of these findings" to satisfy the substantial evidence test). If the examiner is relying on personal knowledge to support the finding of what is known in the art, the examiner must provide an affidavit or declaration setting forth specific factual statements and explanation to support the finding. See 37 CFR

1.104(d)(2).

Accordingly, reconsideration and withdrawal of the rejection of claims 1 and 4 under 35 USC 102(b) is respectfully requested.

Rejection under 35 USC 103(a)

Claims 1-4 stand rejection under 35 USC 103(a) over Vidyadhar '765 in view of Imai '864 or over Sugimoto '841 or Vidyadhar '765 or Imai '864 in view of Lieberman and Brittain. This rejection is respectfully traversed.

The claims are patentable over the combination of Vidyadhar '765 in view of Imai '864 or over Sugimoto '841 or Vidyadhar '765 or Imai '864 in view of Lieberman and Brittain for the following reasons. The framework for the objective analysis for determining obviousness under 35 U.S.C. 103 is stated in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966). Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court are as follows: (A) Determining the scope and content of the prior art; and (B) Ascertaining the differences between the claimed invention and the prior art; and (C) Resolving the level of ordinary skill in the pertinent art. To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385 (CCPA 1970). MPEP 2143.03. It is important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. (KSR v Teleflex, 12 S.Ct. 1727, 1740 (US 2007)). In the instant case, not every element of the claims is taught or suggested in the combination of Vidyadhar '765 in view of Imai '864 or over Sugimoto '841 or Vidyadhar '765 or Imai '864 in view of Lieberman and Brittain.

The Examiner argues that it is unclear what was the basis of applicants' argument in so far as the "elements taught or suggested" by the prior art, and that picking and choosing from the conventional well known solvents taught in the prior art modifying a proven process of making donepezil hydrochloride amorphous form is *prima facie* obvious since such solvents were demonstrated to dissolve donepezil hydrochloride in the prior art and conventionally available in operations such as spray/vacuum drying.

Here, the claims are directed to a process for preparation of amorphous donepezil hydrochloride, which comprises dissolving donepezil hydrochloride in a mixture of an alcohol and a chlorinated solvent; and removing the solvents from the solution; wherein the alcohol is selected from the group consisting of methanol, ethanol, isopropyl alcohol, tert-butyl alcohol and n-butyl alcohol and the chlorinated solvent is selected from the group consisting of chloroform, methylene dichloride, carbontetrachloride and ethylene dichloride.

The Examiner argues that if applicants' argument is that a specific combination of methanol/ethanol to $CHCl_3$ in ratio of 1.2-1 which gives optimum operability in solvent evaporation processes and which is not found in the prior art, then, currently, a requirement of such an element was not found in the claims. Therefore, there is no basis or description supporting the argument and the rejection is proper and maintained.

However, claim 1 recites that he process "comprises dissolving donepezil hydrochloride in a mixture of an alcohol and a chlorinated solvent". This limitation is clearly not disclosed in the Vidyadhar patent. As set forth above, the '765 Vidyadhar patent discloses preparing donepezil free base in methylene chloride, then removing the methylene chloride (see Example 2). In an additional step, the donepezil free base is dissolved in methanol, followed by addition of hydrochloric acid. So, there is not a disclosure in the '765 Vidyadhar patent of a process wherein donepezil hydrochloride dissolved in a mixture of an alcohol and a chlorinated solvent. This deficiency is not addressed by the '864 Imai patent, the Sugimoto '841 patent, or Lieberman and Brittain references.

While the '864 Imai patent discloses several polymorphs of donepezil hydrochloride, it does not teach or suggest a process for preparing amorphous donepezil hydrochloride prepared by dissolving donepezil hydrochloride in a mixture of an alcohol and a chlorinated solvent. The '864 Imai patent does not teach or suggest a chlorinated solvent which is selected from the group consisting of chloroform, methylene dichloride, carbontetrachloride and ethylene dichloride.

Furthermore, there is not a teaching or suggestion in the '841 Sugimoto patent of a process in which donepezil hydrochloride is dissolved in a mixture of an alcohol and a chlorinated solvent. Example 4 of the '841 Sugimoto patent as cited by the Examiner discloses donepezil base dissolved in methylene chloride, to which a 10% solution of hydrochloric acid in ethyl acetate is added, followed by concentration *in vacuo* to obtain a crystal, which was

recrystallized from methanol/isopropyl ether. This deficiency is not addressed by the '864 Imai patent. While the '864 Imai patent discloses several polymorphs of donepezil hydrochloride, it does not teach or suggest amorphous donepezil hydrochloride prepared by dissolving donepezil hydrochloride in a mixture of an alcohol and a chlorinated solvent. The '864 Imai patent does not teach or suggest a chlorinated solvent is chloroform, methylene dichloride, carbontetrachloride or ethylene dichloride.

In addition, there is no motivation for one of skill in the art to alter the methods of the '841 Sugimoto patent, the '765 Vidyadhar patent, or the '864 Imai patent to arrive at the claimed method, and no reasonable expectation of success. There is no teaching or suggestion within the Lieberman and Brittain references to alter the methods as taught by the '841 Sugimoto patent, the '765 Vidyadhar patent, or the '864 Imai patent to arrive at the instantly claimed method.

Here, there is not a combination of prior art elements, since no reference, or combination of references, teaches or suggests a process for preparing donepezil hydrochloride wherein donepezil hydrochloride is dissolved in a mixture of an alcohol and a chlorinated solvent and then the solvents are removed from the solution. No reference or combination of references teaches or suggests such a method wherein the chlorinated solvent is chloroform, methylene dichloride, carbontetrachloride or ethylene dichloride. In addition, Applicant has shown that there is not a reason why a person of ordinary skill in the art would be motivated to practice a process for preparing donepezil hydrochloride wherein donepezil hydrochloride is dissolved in a mixture of an alcohol and a chlorinated solvent and then the solvents are removed from the solution.

Accordingly, reconsideration and withdrawal of the rejection of pending claims 1-4 is respectfully requested.

* * *

For at least the reasons set forth above, it is respectfully submitted that the above-identified application is in condition for allowance. Favorable reconsideration and prompt allowance of the claims are respectfully requested.

Should the Examiner believe that anything further is desirable in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

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August 24, 2009

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Please charge or credit our Account No. 03-0075 as necessary to effect entry and/or ensure consideration of this submission.